

The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: A position statement

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Summary: *N*-Butyldeoxynojirimycin (NB-DNJ, miglustat 'Zavesca') is an orally active iminosugar which inhibits the biosynthesis of macromolecular substrates that accumulate pathologically in glycosphingolipidoses. Clinical trials of NB-DNJ in patients with Gaucher's disease demonstrate the therapeutic potential of such substrate inhibitors in the glycolipid storage disorders. However, macrophage-targetted enzyme replacement using intravenous mannose-terminated human glucocerebrosidase (imiglucerase, Cerezyme) is highly effective in ameliorating many of the manifestations of Gaucher's disease and is a treatment in widespread use. Given that imiglucerase and miglustat are now both licensed for the treatment of Gaucher's disease, there is a need to review their therapeutic status. Here the treatment of type 1 (non-neuronopathic) Gaucher disease is evaluated with particular reference to the emerging role of oral *N*-butyldeoxynojirimycin (miglustat) as a substrate-reducing agent. This position statement represents the consensus viewpoint of an independent international advisory council to the European Working Group on Gaucher Disease.

Gaucher disease is the most common glycosphingolipid lysosomal storage disorder. It is a pan-ethnic disease with an estimated 30 000 affected persons worldwide (Cox and Schofield 1997). An Australian study indicated a frequency for Gaucher disease of 1 per 57 000 live births (Meikle et al 1999), thus predicting a much increased global disease prevalence.

In type I (non-neuronopathic) Gaucher disease, partial deficiency of the lysosomal enzyme glucocerebrosidase results in the accumulation of glucocerebroside, mainly in the cells of the macrophage system. Enzyme replacement therapy (ERT), using mannose-terminated recombinant human glucocerebrosidase, targets the macrophage system, which is the principal site of substrate storage and focus of the disease. ERT with alglucerase and imiglucerase has been successful in the treatment of type I Gaucher disease in adults and children (Barton et al 1991; Beutler et al 1995a; Grabowski et al 1995; Hollak et al 1995; Pastores et al 1993; Zimran et al 1994, 1995). It has offered definitive correction of the underlying enzyme deficiency with amelioration, and in some cases almost complete reversal, of the clinicopathological effects of the disease. ERT reduces organomegaly, improves haematological parameters and has a positive impact on health-related quality of life (Masek et al 1999). Established avascular necrosis of bone does not respond to ERT, but a reduction in pathological marrow infiltrates often leads to slow but substantial improvement in skeletal integrity and bone pain (Hollak et al 2001; Poll et al 2002; Rosenthal et al 1995). However, longstanding complex osseous and pulmonary complications of Gaucher disease may remain refractory to ERT and complete arrest of bone involvement is not established in all cases (Beutler et al 1995a, 1995b, 1996; Elstein et al 1996; Rosenthal et al 1995). Moreover, since ERT does not appear to pass the blood-brain barrier, it has limited ability to improve neurological signs.

Although generally well tolerated, ERT requires regular infusion by the intravenous route and continued compliance in some patients, especially those with early remission

of symptoms, can be difficult to secure. In rare instances, compliance has also been influenced by needle phobia or restricted venous access. Studies of the natural history of untreated Gaucher disease in several groups indicates that, once established, the condition shows variable stability and deteriorates in some but not all symptomatic individuals (Giraldo 2000; Maaswinkel-Mooij et al 2000; Zimran et al 1992). Cessation of therapy or decreased frequency of enzyme infusions has, in some instances, been accompanied by little obvious recurrence of clinical disease (Elstein et al 2000). However this has not been the experience in all populations and the advisability of stopping or reducing enzyme therapy is questionable (vom Dahl et al 2001; Weinreb 2001).

Treatment with alglucerase and imiglucerase therapy is expensive and access to enzyme therapy is not guaranteed for all patients in whom it is required. In type III (chronic neuronopathic) Gaucher disease, enzyme therapy clearly improves visceral and haematological manifestations, but neurological deterioration can sometimes occur despite administration of high-dose enzyme therapy (Vellodi et al 2001); therefore, there may be a case for an adjunctive therapy to be administered as well as enzyme for this form of Gaucher disease.

N-Butyldeoxynojirimycin (NB-DNJ) (miglustat, OGT 918, Zavesca) offers an alternative approach to the treatment of Gaucher disease based on the concept of substrate reduction therapy (SRT). In this disease the effect of NB-DNJ is indirect in that it reduces the burden of glycolipids delivered to the macrophage system after phagocytosis of formed blood cells. This approach, first advocated by Radin and colleagues (Inokuchi and Radin 1987) seeks to retard the formation of glycosphingolipids to rates at which the residual enzyme activity can catabolize stored and incoming lysosomal substrate (Conzelmann and Sandhoff 1983). NB-DNJ is an inhibitor of the ceramide-specific glucosyltransferase that initiates the glycosphingolipid biosynthetic pathway and catalyses the formation of glucocerebroside.

Experiments conducted with an *in vitro* model of Gaucher disease demonstrated that NB-DNJ prevented the lysosomal storage of glucocerebroside and the compound was thus proposed for clinical use in glycosphingolipid disorders (Platt et al 1994). Clinical trials demonstrated that an NB-DNJ prodrug was tolerated for up to 6 months at doses up to 3 g daily when used as an α -glucosidase-1 inhibitor in an attempt to decrease viral burden in patients with HIV-1 infection (Fischl et al 1994; Tierney et al 1995). There were safety concerns, although assessment of the relationship of the symptoms that developed in the patients and the study drug was confounded by the nature of the illness under consideration. In trial patients receiving the drug in combination with nucleoside-based antiretroviral agents, paresthesias were noted, although no definitive evidence of peripheral neuropathy was reported and the incidence of these symptoms was not significantly greater than in patients receiving antiretroviral therapy alone.

A recent one-year open-label study has shown that decreased substrate formation by NB-DNJ gradually improves key clinical features of type I Gaucher disease including liver and spleen volumes, haematological variables and plasma chitotriosidase activities (Cox et al 2000), although some adverse events were reported.

In the light of these findings and further clinical trial results, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMA) adopted a positive opinion, recommending the granting of marketing authorization for NB-DNJ, now known as miglustat (Zavesca) for oral treatment of mild-to-moderate type I Gaucher disease if ERT is not suitable. The categories of mild and moderate severity of Gaucher disease are based arbitrarily on clinical criteria and laboratory parameters, which could include a haemoglobin count greater than 9 g/dl, platelet count greater than $50 \times 10^9/L$ and no evidence of progressive osseous disease. Recourse to the severity score index proposed by Zimran and colleagues may provide a more objective means to define these categories (Zimran et al 1992).

This marketing authorization has now been granted and the summary of product characteristics gives the following recommendations on the approved indication of miglustat:

1. For the oral treatment of mild-to-moderate type I Gaucher disease.
2. To be used only in the treatment of patients for whom ERT is unsuitable.
3. Treatment to be directed by physicians who are knowledgeable in the management of Gaucher disease.
4. Use in children and adolescents is not recommended.

Since preclinical testing in rats showed that the agent affected spermatogenesis, it was stated that male patients should use reliable contraceptive methods while taking the drug. In addition, miglustat should not be used during pregnancy or breast-feeding. Contraceptive measures should be used by women of child-bearing potential. (For further details, refer to the Zavesca summary of product characteristics.)

A European Advisory Council consisting of leading experts in the field, including representatives from patient organizations, was gathered under the auspices of the European Working Group on Gaucher Disease (EWGGD) to consider the therapeutic position of SRT with NB-DNJ (miglustat). The Advisory Council's objective was to analyse published and unpublished data and present recommendations on this agent's role in the treatment of type I Gaucher disease.

DEFINITIONS AND DIAGNOSIS

Gaucher disease is clinicopathological syndrome in which storage of glucocerebroside occurs principally in mononuclear phagocytes and is caused by deficiency of the lysosomal enzyme glucocerebrosidase (acid β -glucosidase, EC 3.2.1.45). It is inherited as an autosomal recessive disorder. Most of the storage material is derived from exogenous membrane components released by phagocytosis of haematopoietic cells (Brady 1978). The clinical features of the condition principally reflect the distribution of abnormal macrophages (Gaucher cells) within affected organs and tissues.

Gaucher disease is a multisystem disorder associated with striking variation in its clinical manifestations, severity and course. Three phenotypes of Gaucher disease, based on the presence or absence of neurological symptoms, were first proposed in 1962 (Knudson and Kaplan 1962). Type I Gaucher disease, McKusick 230800, is caused by partial glucocerebrosidase deficiency with no discernible neuronopathic manifestations such as gaze palsies, ataxia, seizures or cognitive disturbances. It is associated principally with parenchymal disease of the liver, spleen, bone marrow and, in severe cases, the lung. Mutations in the glucocerebrosidase gene that severely affect its function are additionally associated with neurological manifestations (acute neuronopathic Gaucher disease (type II, McKusick 230900) and chronic neuronopathic Gaucher disease (type III, McKusick 231000), respectively).

Typical manifestations in type I Gaucher disease include fatigue, splenomegaly, hepatomegaly, and osseous manifestations (including osteopenia/osteoporosis, avascular necrosis and lytic lesions of bone) (Cox and Schofield 1997). Hypersplenism can lead to anaemia, bleeding due to thrombocytopenia and recurrent bacterial infection associated with neutropenia.

Knowledge of the genotype allows limited prediction of the severity of disease. For instance, certain mutations indicate that the patient has severe disease (e.g. homozygosity for L444P). Other mutations, such as the N370S allele are almost never associated with neuronopathic disease and the presence of one copy of this allele is almost invariably associated with type I Gaucher disease (Beutler and Gelbart 1996; Grabowski and Horowitz 1997).

However, while mutations, in the human glucocerebrosidase gene are necessary for the development of the condition, they are not tantamount to, or sufficient for, a diagnosis of symptomatic Gaucher disease. Homozygosity or compound heterozygosity for some mutant alleles of glucocerebrosidase may be detected in otherwise asymptomatic or apparently healthy people. Thus, clinical expression of the disease cannot be accurately predicted by mutation analysis alone (Boot et al 1997), although knowledge of the glucocerebrosidase genotype may contribute to prognosis and provide a broad guide to clinical behaviour (Levy-Lahad and Zimran 1997).

A demonstration of Gaucher cells in bone marrow aspirate can lead to misdiagnosis, even when combined with clinical symptoms typical of the disease. Gaucher-like cells have been described in a number of other conditions, including multiple myeloma, myeloid leukaemia, thalassaemia and Hodgkin disease (Beutler and Grabowski 2001). Therefore, histological examination of the spleen, bone marrow and other organs is insufficient for the definitive diagnosis of Gaucher disease.

Biochemical and molecular techniques are more specific and less invasive. In patients with symptoms associated with evidence of tissue injury, the definitive diagnosis of Gaucher disease requires the demonstration of deficient glucocerebrosidase activity in mixed leukocyte preparations or fibroblast cultures. Most patients with Gaucher disease have demonstrated glucocerebrosidase activity $\leq 15\%$ of mean normal activity (Brady et al 1965).

MONITORING

Patients with type I Gaucher disease require a range of assessments that include the following.

1. **Detailed medical history** (increased fatigue, bone pain, bruising/bleeding, abdominal distension/pain, depression, recent weight loss, shortness of breath, reduced range of joint movements). The family history is clearly important in this autosomal recessive disease.
2. **Clinical examination** at least every 6–12 months (liver and spleen size, heart and lungs, bone and joint pain, bruising, skin (cutaneous signs of haemorrhagic tendency with purpura or ecchymoses), growth retardation in children).
3. **Laboratory investigations:** full blood counts, haemoglobin concentration, biochemical markers including angiotensin-converting enzyme (ACE), tartrate-resistant acid phosphatase (TRAP), chitotriosidase, ferritin, serum liver related tests, serum immunoglobulins and electrophoresis, urea and electrolytes. There appears to be a higher than expected prevalence of monoclonal gammopathy and deficiency of vitamin B₁₂ in Gaucher disease and periodic monitoring for these is advisable (Aerts and Hollak 1997; Cox and Schofield 1997; Gielchinsky et al 2001).
4. **Imaging and other evaluations:** Recommended investigations include, for example: dual energy X-ray absorptiometry (DEXA); skeletal and chest radiology; magnetic resonance imaging (MRI) of viscera and pelvis; abdominal ultrasonography; computerized tomographic (CT) scans (for volume evaluations); echocardiography and pulmonary function tests (to detect pulmonary infiltration and pulmonary hypertension); and QCSI (quantitative chemical shift imaging) to determine marrow infiltration).

TREATMENT

Since the early 1990s, ERT administered by intravenous infusion is the cornerstone of treatment for Gaucher disease. Recent marketing authorization of oral NB-DNJ for patients who are unsuitable for ERT offers a potential alternative to clinicians and will be considered in detail in this section.

Enzyme replacement therapy

ERT with mannose-terminated recombinant human glucocerebrosidase imiglucerase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA) occupies a primary position in the treatment of Gaucher disease. ERT has been shown to ameliorate systemic involvement in type I Gaucher disease and enhances quality of life.

The treatment has an outstanding record of safety and acceptability for most patients with symptomatic Gaucher disease. Rare instances of immune reactions or hypersensitivity to alglucerase and imiglucerase preparations have occurred (Germain et al 2001; Grabowski et al 1995; Richards et al 1993).

Widely divergent views have been expressed on the optimal dosage of imiglucerase for ERT. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy (Barton et al 1991; Grabowski et al 1995; Zimran et al 1994). Administration of doses as low as 1.15 U/kg of body weight three times a week (Hollak et al 1995) or 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly. High-frequency regimens are not, however, in widespread use. Dosage should be individualized for each patient according to treatment responses during monitoring.

Recent data from the International Collaborative Gaucher Group show that most patients treated with ERT achieve normal haemoglobin levels within 2 years of initiation of treatment (Weinreb et al 2002). This study in over 1000 patients with type I Gaucher disease in the Gaucher Registry concluded that platelet counts increase in patients with or without spleens within the first 6 months and are sustained or increased for up to 5 years. Liver and spleen sizes decrease by 20–30% within 1–2 years of treatment initiation, with reductions of 30–40% by 5 years.

Substrate reduction therapy

A decrease of substrate formation by NB-DNJ has been demonstrated to be effective in improving clinical features of type I Gaucher disease including haematological parameters and organomegaly (Cox et al 2000).

Efficacy: The marketing authorization of NB-DNJ has been based on three trials, of which two have been published (Cox et al 2000; Heitner et al 2002). The first study was an open-label, noncomparative, multicentre study of NB-DNJ 100 mg t.i.d. in 28 patients who were unable or unwilling to receive ERT (Cox et al 2000). At 12 months, mean liver and spleen volumes were 12.1% and 19.0% lower than at baseline ($p < 0.001$). These improvements have continued at 24 and 36 months in the liver (14.5% and 17.5% reduction from baseline, respectively; $p < 0.001$) and spleen (26.4% and 29.6% reduction from baseline, respectively, $p < 0.001$) in an extended study which enrolled 18 patients. From months 6 to 24 there were statistically significant mean decreases in percentage chitotriosidase activity from baseline ($p < 0.05$). At 12 months the mean increase in haemoglobin was 0.26 g/dl and the platelet count was $8 \times 10^9/L$. This was maintained at 24 and 36 months with mean increases of 0.9 g/dl and $14 \times 10^9/L$, and 0.9 g/dl and $22 \times 10^9/L$ respectively ($p < 0.05$; $p < 0.001$).

Another study randomized 36 patients who had received a minimum of 2 years' ERT into three treatment groups: continued ERT, combination therapy with ERT and NB-DNJ, and switch from ERT to NB-DNJ (Elstein et al 2002). Patients switched to NB-DNJ had their disease control maintained as determined by small reductions in liver and spleen organ volume. However, there were reductions in platelet count and increases in chitotriosidase activity in some patients, indicating that NB-DNJ monotherapy might not be sufficient to maintain the same control of disease activity in all patients. Those on combination therapy showed mean liver volume reduction of 4.9% and mean spleen volume reduction of 8.5%. As might

be expected, patients in this study found the oral regimen of miglustat to be more convenient than intravenous infusion of ERT. Quality of life measures and these clinical findings indicate the efficacy of NB-DNJ as oral monotherapy in type I Gaucher disease.

A further study to assess the tolerability and efficacy of a lower dose of NB-DNJ established that a dose of 100 mg t.i.d. offers improved clinical efficacy when compared with 50 mg t.i.d. with no difference in the incidence of adverse events (Heitner et al 2002). At present there are no data available on the use of NB-DNJ in patients younger than 18 years or older than 80 years.

Adverse effects:

Preclinical toxicity studies. Gastrointestinal effects were the most frequent adverse effects in pre-clinical studies of NB-DNJ. Weight loss, considered to be due to fat reduction, was seen in all studies. No toxicity has been demonstrated in several pre-clinical studies of the central and peripheral nervous system or in juvenile animals.

Clinical studies. Diarrhoea: In clinical studies the most frequent adverse event was diarrhoea. Early in treatment nearly all patients complained of some degree of diarrhoea (including an increase in frequency and some loosening of the stool). However, over time the prevalence decreased to within levels reported previously for patients with Gaucher disease (Damiano et al 1998). Most cases of diarrhoea are mild and resolve spontaneously or after dose reduction.

Weight loss: Approximately 60% of patients lose weight, with a mean weight loss of 6–7% at 12 months which is recovered by 24 months of treatment.

Tremor: Approximately 30% of patients have reported tremor that resolved spontaneously on treatment as well as on withdrawal of treatment or lowering of the dose.

Peripheral neuropathy: Rare cases of peripheral neuropathy associated with paraesthesias and burning sensations have been described in patients treated with NB-DNJ. There is a need to determine the frequency of these abnormalities in an untreated cohort of patients with the disease.

Cognitive function: Disturbed cognitive function was observed in a single elderly patient in whom the possible relationship to NB-DNJ was considered to be unlikely.

Surveillance: Baseline and periodic assessment of cognitive function and peripheral neuropathy is recommended in all patients receiving NB-DNJ. An unexpected finding, subsequent to the report of peripheral neuropathy, has been the prevalence of electrodiagnostic abnormalities and peripheral nerve disturbances in patients with Gaucher disease who are either receiving ERT or are untreated. The EWGGD has initiated an ongoing surveillance study at the request of the EMEA to assess the background frequency of these abnormalities and cognitive functions in the Gaucher population. Furthermore, a long-term pharmacovigilance monitoring programme for those patients receiving NB-DNJ has been established by the regulatory authority.

Indications:

The preferred treatment providing the best standard of care for all patients with Gaucher disease is ERT. Some patients with mild-to-moderate type I Gaucher disease may be unable or may not wish to receive ERT. Under these conditions, administration of NB-DNJ may be appropriate. In the context of the licensed indications for oral NB-DNJ treatment, the Advisory Council considered the following patient categories to be eligible for treatment with NB-DNJ:

1. Patients naive to treatment, with mild or moderate symptomatic Gaucher disease who are unwilling or unable to receive ERT for medical or personal reasons (see below).
2. Patients who are unsuitable (unwilling or unable to continue) for ERT. Examples include those with needle phobia, persistent difficulties with infusion, poor compliance with therapy, poor venous access, religious reasons, occupations or travelling arrangements that make it difficult for them to receive regular intravenous infusions, and those who experience infusion reactions.
3. Patients with persistent signs of disabling disease activity despite maximum achievable dosing with ERT (noting that miglustat has yet to be tested in severe Gaucher disease but also that the product license for miglustat does not preclude its co-administration with ERT). For patients in this category, the drug may be given in combination with ERT with frequent monitoring of response.

In addition, the Advisory Council recommended that:

- NB-DNJ should only be prescribed for adults by experts, based in dedicated centres, who are familiar with the treatment of Gaucher disease or after detailed consultation with such experts.
- Recommendations by physicians for the use of NB-DNJ rather than ERT at any stage of disease activity should be based on clinical criteria alone and not related to issues of potential cost.
- A discussion of potential adverse effects of NB-DNJ requiring safety monitoring, compared with imiglucerase, should be undertaken with the patient before the drug is prescribed.
- The safety and efficacy of NB-DNJ for patients with severe Gaucher disease (i.e. those with haemoglobin 9 g/dL or less, platelet count $50 \times 10^9/L$ or less, and rapidly evolving osseous disease) has not been established.

Based on the existing data, the Advisory Council recommended a treatment algorithm for the use of NB-DNJ (Figure 1).

THE ROLE OF PATIENT ORGANIZATIONS

The Advisory Council of the EWGGD recognizes the key role of European patient organizations that represent patients invited by EMEA to participate in the surveil-

lance programme. Representatives of these organizations from each of the main constituent countries were invited to contribute to the discussions and presentations by the Advisory Council. A list of attenders and their affiliations is given below following the position statement.

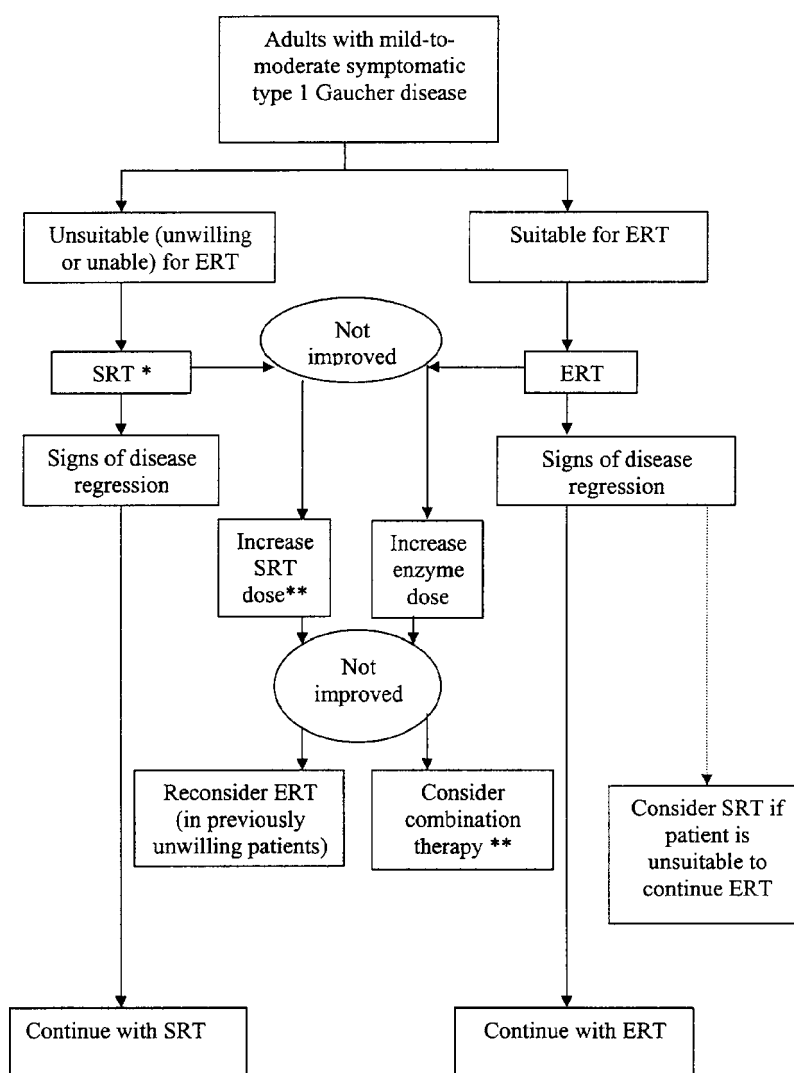


Figure 1 Treatment algorithm for Gaucher disease. *SRT is contraindicated in pregnancy and in men wishing to start a family. **These actions have not been validated by trial experience

POSITION STATEMENT

- Substrate reduction therapy with the approved iminosugar preparation NB-DNJ (miglustat) has demonstrated efficacy in nonsevere type I Gaucher disease. Although enzyme replacement represents the first-line treatment for Gaucher disease, miglustat provides an effective alternative in adults unsuitable (unwilling or unable) for enzyme therapy.
- Expert members of the European Working Group on Gaucher disease (EWGGD) recommend that if NB-DNJ (miglustat) is considered suitable for use in adult patients with type I Gaucher disease, it should only be given by physicians experienced in the diagnosis and treatment of this disorder, and after full consideration of its therapeutic position as set out in this position statement.
- Upon licensing of NB-DNJ (miglustat) by the European Agency for the Evaluation of Medicinal Products (EMA) an ongoing programme of pharmacovigilance has been instituted. At the same time, a survey will take place under the auspices of the EWGGD to detect any possible excess of neurological events in the population of patients with Gaucher disease receiving NB-DNJ (miglustat) compared with the population of patients who have not taken this agent. Access to this information will be made available at EWGGD meetings and, it is envisaged, by published updates.

Notes

- This position statement was compiled with complete editorial freedom. A small unrestricted educational grant was provided by Oxford GlycoSciences (UK) Ltd and used by the panel of authors solely for co-ordination and communication.
- Currently available enzyme replacement therapy (ERT) refers to treatment with the modified placental human glucocerebrosidase, alglucerase (Ceredase, Genzyme Corporation, Cambridge, MA, USA) or the recombinant human glucocerebrosidase preparation, imiglucerase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA)
- Currently available substrate reduction therapy (SRT) refers to treatment with *N*-butyldeoxynojirimycin (miglustat, Zavesca, formerly compound OGT 918 of Oxford GlycoSciences (UK) Ltd).

Patient representatives

Susan Lewis, Gauchers Association, London, UK; Dr Raul Chertkoff, Israeli Gaucher Patients Association, Israel; Ria Guijt, Gaucher Vereniging Nederland; Ghislaine Surrel, Vaincre les Maladies Lysosomales, France; Fernanda Torquati, Associazione Italiana Gaucher, Italy; Ursula Rudat and Michael Pils, Gaucher Gesellschaft Deutschland, Germany; Tanya Collin-Histed, Neuronopathic Gaucher Disease, UK; Jeremy Manuel, European Gaucher Alliance.

(Susan Lewis and Raul Chertkoff are members of the EWGGD Advisory Council.)

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